Regions/ORD Endocrine Disruptors Workshop (Atlanta, GA, May 1-3, 2001), Bobbye Smith, Sophia Serda, and Marion Olsen

Workshop themes included:

- What are uncertainties?
- Science issues and communication
- Mandates and activities to implement
- Addressing uncertainties and mandates
- HH and Eco RAs

What is an endocrine disruptor? It is "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or illumination of natural hormones in the body that are responsible for the maintenance of reproduction, development, and/or behavior." Examples of classes of EDCs exist in all kinds of chemicals including: pesticides, herbicides, insecticides, metals, and pharmaceuticals. The endocrine system consists of the hypothalamus, pituitary and thyroid, in addition to the sex hormones.

Science Policy Council Highlights/Major Conclusions:

- There appears to be a common theme about endocrine disruption both in humans and wildlife.
- Female reproductive effects, as seen in the literature up to October 1995 (however, direct relationships can't be concluded) include
  - endometriosis (etiology unknown; no known correlation with serum levels of halogenated aromatic HCs; recommend evaluating non-primate models), and
  - breast cancer (no clear evidence for organochlorine pesticides, PCBs, or dioxins; cannot assign a single cause; need more animal testing).
- Male reproductive effects include
  - a decrease in sperm counts (still controversial; general widespread reduction not supported)
  - testicular cancer (evidence of an increase but cause unknown), and
  - prostate cancer (cannot discount role of endocrine disruption; some correlation with herbicides and coke oven emissions).
- Hypothalamus and pituitary effects: There is concern about exposure to EDCs during the early stages of development, because many feedback mechanisms are not yet functional. Tests need to consider the role of the brain and the pituitary.
- Thyroid effects: There are well-documented effects from many agents (e.g., urea derivatives, TCDD, polyhalogenated biphenyls).
- Human health effects: The Science Policy Council Panel concluded that "exposure to a single xenoestrogenic compound, under current environmental conditions would be sufficient to develop an adverse effect."
- Ecological effects:
  - There are several well documented aquatic and wildlife ED effects, such as TBT and Imposex/Intersex in gastropods, phytoestrogens, masculinization of fish, and feminization of male birds (gulls).
  - Comparable ED effects data are lacking for many taxa, especially

amphibians.
- Methods are needed for evaluating ecological effects.

The Science Policy Council's Interim Position: "Based on the current state of the science, the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or a mechanism of action potentially leading to other outcomes, for example carcinogenic, reproductive or developmental effects." The EPA regulates endpoints, but not endocrine disruptors.

OPPTS ED Screening Program implementation drivers include:
- a Food Quality Protection Act (FQPA) mandate, and
- a requirement to present a FY 2000 report to Congress on the Endocrine Disruption Screening Program (EDSP). The data in this report is not to be used for RA!

Phase I: There are 87,000 chemicals that OPPT expects to screen, with specific strategies for dealing with pesticides.

Endocrine disruptor priority setting database will involve
- ranking chemicals based on existing exposure and effects information and data, such as
  - exposure compartments (use frequency of occurrence, concentration or quantity to rank chemicals),
  - effects compartments (LOAEL or NOAEL),
  - QSARs to assist chemical ranking, and
  - ranking chemicals on exposure and effects separately and combined; and
- focusing on the commodity chemicals.

Priority setting for pesticides:
- sort and prioritize "other" (inert) ingredients using EDPSDB
- run pilot program for 25-50 (already-registered) active ingredients
- develop criteria to examine existing data
- utilize criteria, re-registration and tolerance reassessment schedules to set priorities

Currently, ORD is prioritizing the chemicals and the validation phase is expected to be completed by 2003. The screening data are expected in 2004, with the implementation phase beginning in 2005.

EDC Test Protocols:
- Tier 1 Tests: screening assays such as receptor binding assays (ER and AR)
- Tier 2 Tests: multi-generation tests for mammalian, avian, fish (promising), and amphibian (promising) development and reproduction, and the mysid shrimp life cycle.

Major EDC uncertainties include:

- exposure-outcome linkages (don't know much about them), such as
  - latency in expression,
  - persistent vs. non-persistent contaminants,
  - fate and transport, and
  - weffects are occurring in humans;
- chemical diversity, because
  - there are about 100 chemicals with different structures and potency, including phytoestrogens, and
  - it is uncertain what EDSP will tell us; and
- multiple effects.

Elements of ORD's research plan based on the RA paradigm include
- exposure studies, and
- effects studies.

There is a need for ORD/NERL EDC exposure method development, refinement, and adaptation. ORD currently has an approved protocols for measuring endocrine disrupting chemicals in sediments, water and waste water.

ORD/ NHEERL EDC HH risk information developed post 1995 has been for
- PCBs,
- dioxins for
  - nearly all vertebrate animals examined respond to dioxin, including
    - humans, which have the Ah receptor, and the other members of its signaling complex, and
    - human cells; and
  - dioxin body burdens (ng/kg) associated with adverse effects, including
    - developmental neurotoxicity (42),
    - developmental reproductive toxicity (28-73),
    - developmental immunotoxicity (50), and
    - adult immunotoxicity (10);
  - non-cancer dioxin effects from empirical modeling (lowest ED_{01}); and
  - cancer dioxin effects from
    - linear models, and
    - excess risk to background population, which is
      - about 10^{-3}, and
      - assumes mean body burden.

Are IRIS numbers protective of endocrine disruptor effects? It is assumed that they are, because they are supposed to be protective of cancer effects.

The results of all of the tests will soon be posted on the Intranet.

ORD/NHEERL EDC Ecological Receptor Effects Research:
- Focus Area 1: development and standardization of protocols to identify EDCs
- Focus Area 2: developmental exposure and consequences

Why screen EDCs with crustaceans (Mysid shrimp)?

- They are a dominant non-target organism.
- They have similar structure to insect and crustacean hormones and a reference juvenile hormone analogue used as a pesticide.

The organisms are exposed and have continuous exposure throughout the test (20 days for first part). After the first 20 days, the exposure is discontinued. Endpoints measured are the number of eggs, viability, and reproductive effects.

Why screen EDCs with fish? Widespread effects due to EDCs could be affecting this class of animals.

Research: Bioassays for identification of EDCs in fish include

- *in vitro* assays and QSAR Modeling
  - Advantages: rapid and inexpensive; reflective of specific mechanisms/pathways of concern
  - Disadvantages: not necessarily representative of a field response; limited response
- *in vivo* assays with fatheads and cunner, which has the application of screening for endocrine "activity" (measure 'endocrine axis').

ED Workshop science communication activities:

- discussing how to use and communicate upcoming EDSTAC data to the scientific community and the public
- developing answers to frequently asked questions for risk assessors

Stakeholder concerns include the

- effects of EDs on thyroid and reproductive systems,
- impacts to children *in utero* or during breast-feeding,
- the unknown effects of EDs,
- differences in scientific opinion, and
- the protectiveness of cleanup goals.

Summary:

- ORD is currently validating EDSTAC testing protocols.
- Data generated to date has not changed EPA policy/position on endocrine disruptors.
- EDSTAC screening tests are not designed for Superfund risk assessment.

Contact Information: www.epa.gov/opptintr/chemrtk/bolchall.htm is OPPTS' website for endocrine disruptors